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NEPHROLOGY FORUM

Uric acid and calcium oxalate nephrolithiasis

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Case presentation

A 33-year-old man was examined because he formed recurrent renal calculi. At age 22, he had been hospitalized and had undergone ureterolithotomy for a right-sided calculus composed of calcium oxalate monohydrate and uric acid. During the ensuing 11 years, he passed 12 new stones, for which he was hospitalized eight more times, underwent five cystoscopic procedures for stone removal, and had two more ureterolithotomies, one on each side. His most recent x-ray films disclosed three renal stones, of which two were on the left. Of the nine that had been passed or removed, four were mixtures of calcium oxalate and uric acid, three were pure calcium oxalate, and two were pure uric acid. The remainder of his medical history was negative. His diet was unremarkable except for a daily one-pound total intake of meat, fish, and poultry.

Physical examination was within normal limits; the patient weighed 82.3 kg. Blood concentrations of calcium, uric acid, and creatinine were normal. Three 24-hr urine samples were collected on an outpatient basis while he followed his regular diet (Table 1). Urine calcium excretion exceeded the normal upper limit of 300 mg/day for men, and uric acid excretion exceeded the normal upper limit of 800 mg/24 hr. Urine concentration of undissociated uric acid was uniformly above the solubility limit in urine, which is 96 ± 2 mg/liter. His urine was supersaturated 3.65- to 4.71-fold above the solubility product. The degree of supersaturation with respect to calcium oxalate monohydrate was determined by incubating an aliquot of each urine sample for 48 hr at 37°C with 5 mg/ml of crystalline calcium oxalate monohydrate. The ratio of the calcium oxalate concentration product before the incubation to that after the incubation, termed the concentration product ratio (CPR), provides a measure of supersaturation, the units of which are multiples of the solubility product [1].

The patient was advised to eat a specified diet designed to provide 2 mg of calcium per kg body weight daily. The daily diet contained a total of 9 ounces of meat, fish, and poultry; grains, fats, starches, and vegetables made up the additional calories. His weight remained unchanged at 82 kg. Studies of the urine on days 7, 8, and 9 of this diet revealed that the calcium excretion exceeded calcium intake on each of the 3 days (Table 2). Uric acid excretion fell to normal (<800 mg/24 hr), and undissociated uric acid concentration declined to levels approaching the solubility limit in urine.

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Discussion

DR. FREDRIC L. COE (*Director, Nephrology Program and Professor of Medicine and Physiology, University of Chicago Pritzker School of Medicine, Chicago, Illinois*): Two different crystals, uric acid and calcium oxalate, produced severe stone disease in this patient. Some of his calculi were composed exclusively of one of the crystals, whereas other stones were composed of both. Most patients produce only calcium stones; in our experience, only 11% of patients develop mixed types (Table 3); rarer still are the few patients whose stones are pure uric acid. One might think that each crystal forms because of a distinctive urine chemistry disorder that may require treatment, and as far as I can tell, this usually is the case.

Production of uric acid stones

Urine pH. Uric acid has two dissociable protons. The first has a dissociation constant (pKa) of 5.35 in urine at 37°C [2]. Hydrogen urate, the product of uric acid dissociation, forms salts in urine mainly with sodium, potassium, and ammonium. Stones of sodium- or potassium-hydrogen urate are unknown, and those of ammonium hydrogen urate are rare, but stones of uric acid form easily. Undissociated uric acid itself is soluble in human urine only up to concentrations of 96 ± 2 mg/liter at 37°C [3]. The nomogram shown in Figure 1 can be used to estimate uric acid supersaturation from 24-hr urine pH and the total uric acid concentration (T), the quantity actually measured by the clinical laboratory.

Table 1. Urine studies of the patient under discussion[a]

Measurement	Day 1	Day 2	Day 3
Volume *(ml/24 hr)*	1560	1290	1475
Creatinine *(mg/24 hr)*	1675	1710	1689
Calcium *(mg/24 hr)*	398	347	455
Oxalic acid *(mg/24 hr)*	36	41	38
Uric acid *(mg/24 hr)*	982	1027	914
pH	5.72	5.64	5.81
Undissociated uric acid *(mg/liter)*	268	408	215
CPR *(CaOx)*[b]	4.71	3.65	4.26

[a] Studies were performed with the patient following his regular diet.
[b] CPR refers to concentration product ratio; CaOx refers to calcium oxalate monohydrate.

Table 2. Urine studies of the patient under discussion[a]

Measurement	Day 7	Day 8	Day 9
Volume *(ml/24 hr)*	1600	1590	1375
Creatinine *(mg/24 hr)*	1640	1678	1670
Calcium *(mg/kg/24 hr)*	3.72	3.64	3.80
Uric acid *(mg/24 hr)*	755	743	760
pH	5.95	6.12	6.0
Undissociated uric acid *(mg/liter)*	118	79.4	124

[a] Studies were performed during the last 3 of 9 days that the patient followed a low-calcium diet. Calcium intake on days 7, 8, and 9 was 2.1, 1.94, and 2.0 mg/kg/24 hr, respectively.

Figure 1 also illustrates how urine pH predominates over urine volume and total uric acid concentration in determining undissociated uric acid concentration and, therefore, in predisposing to the formation of uric acid stones. When pH is below 5.5, urine volume must be nearly 2 liters to dissolve 600 mg of uric acid, the amount excreted by a normal man [4]; whereas when urine pH exceeds 6.0, even massive hyperuricosuria is unlikely to cause supersaturation.

Clinical experience supports this reasoning (Table 3). In our patients, urine pH was appreciably lower in uric acid stone formers than it was in patients with other kinds of stones. Moreover, low urine pH in uric acid stone formers was associated with higher values for undissociated uric acid supersaturation. The urine of patients who produced only calcium stones generally was not supersaturated with respect to uric acid, whereas the urine of patients who formed both calcium oxalate and uric acid stones was moderately but definitely supersaturated; this difference was attributable to differences in urine pH. The patient presented today excreted urine that was excessively supersaturated with respect to uric acid (Table 1) because of *both* low pH and hyperuricosuria.

Urine pH over the course of a typical day is abnormally low in patients with gout [5] as it is in patients with a hereditary predisposition to forming uric acid stones [6]. The explanation for aciduria in these conditions is unknown. Diseases of the intestine and possibly of the kidney also can lower urine pH. In small bowel disease or after ileostomy, bicarbonate is lost in the stool, and renal acid excretion must rise to preserve systemic acid balance. Diet also influences urine pH; for example, a high intake of meat provides considerable methionine, the sulfhydryl of which is oxidized to sulfuric acid, a strong urinary acidifier [7]. When today's patient ate less meat, he produced a less acid urine that was also less supersaturated (Table 2).

Uric acid excretion. Hyperuricosuria itself can contribute to uric acid stones by raising total uric acid concentration (Fig. 1). Without some concomitant reduction of average urine pH, however, hyperuricosuria rarely causes stones unless it is massive. Tumor lysis, myeloproliferative disorders, and hereditary conditions characterized by uric acid overproduction [8] can raise urine uric acid excretion to 1000 or even 2000 mg daily. Under these circumstances, the solubility limit for undissociated uric acid can be exceeded even when urine pH is as high as 6.0; acute and massive hyperuricosuria can cause intratubular uric acid precipitation and acute renal failure [9]. Daily uric acid excretion is not routinely elevated in the usual patient with uric acid lithiasis; only 9 of our 22 patients were hyperuricosuric (Table 3) [10]. However, modest hyperuricosuria is more frequent in stone formers, even those who form calcium oxalate stones, than in normal people [3, 4, 11]. Dietary purine excess from meat is probably responsible. The potential for uric acid precipitation is compounded because urine pH is slightly lower than normal in patients who eat large quantities of meat [3, 12]. In today's patient, hyperuricosuria disappeared when dietary meat intake was reduced (Table 2).

Production of calcium oxalate stones

Hypercalciuria in stone patients. The most dramatic difference between people who form calcium oxalate stones and those who do not is that most stone formers excrete more calcium in their urine [13], even though the serum calcium concentrations are normal. The tendency towards normocalcemic hypercalciuria appears to be genetic [14]. Among people who have never produced a stone, urine calcium excretion spans a wide range, the upper end of which overlaps with the range of values occurring in stone formers [15]; thus, stone formers appear as though they had been selectively culled from the upper tail of the normal distribution, over 50% having calcium excretion rates that occur in less than 10% of normals. Our cutoff for distinguishing between normal calcium excretion and hypercalciuria, expressed as the amount of calcium excreted in 24 hr, is 300 mg for men and 250 mg for women, or 4 mg/kg in either sex [16].

Although convenient, this definition of hypercalciuria obviously is arbitrary. A more insightful approach is to determine, for every level of calcium excretion, the likelihood of its indicating a normal individual or a stone former. We studied patients who were under treatment for recurrent stone disease. Most remained stone-free; some went on to form more stones. The technique of discriminant analysis allowed us to calculate the relationship between a given calcium excretion rate and the risk of forming a new stone. Using this technique, the 50% probability point, which gives the dividing line between the two groups, was found to be 2.4 mg/kg/24 hr, a value within the usual range of normal [17]. The patient presented today excreted between 4.2 and 5.54 mg/kg of calcium daily, far above the threshold of risk.

Hypercalciuria could increase the risk of calcium stone formation by raising urine supersaturation with respect to calcium oxalate. We [1] and others [18] have observed that urine from patients with hypercalciuria was more highly super-

Table 3. Selected laboratory measurements in patients with calcium, uric acid, or mixed stones[a]

	Types of stones		
	Calcium (N = 821)	Mixed (N = 109)	Uric acid (N = 22)
Serum determinations			
Creatinine *(mg/dl)*	.98 ± .01	1.02 ± .02[b]	1.06 ± .05
Uric acid *(mg/dl)*	5.70 ± .04	6.38 ± .14	5.96 ± .33
Calcium *(mg/dl)*	9.48 ± .01	9.55 ± .43	9.35 ± .06[c]
Phosphorus *(mg/dl)*	3.17 ± .48	3.23 ± .62	3.25 ± .08
Urine determinations			
Volume *(liter)*	1.59 ± .06	1.53 ± .05	1.51 ± .12
Calcium *(mg/24 hr)*	231 ± 4	216 ± 10	175 ± 25
(mg/kg/24 hr)	3.06 ± .05	2.62 ± .12[d]	2.12 ± .28[e]
Uric acid *(mg/24 hr)*	700 ± 40	665 ± 20	669 ± 40
pH	6.0 ± .4	5.7 ± .4[e]	5.5 ± .4[e]
Oxalate *(mg/kg/24 hr)*	39 ± 16	38 ± 1	36 ± 3

[a] All values are mean ± SEM. Reprinted from *Kidney International* (Vol. 22, 1982 with permission) [10].
[b] Differs from calcium, $P < .05$.
[c] Differs from mixed, $P < .05$.
[d] Differs from calcium, $P < .01$.
[e] Differs from calcium, $P < .001$.

saturated with respect to calcium oxalate monohydrate than was normal urine (Fig. 2). Today's patient exhibited supersaturation between 3.65- and 4.71-fold, levels considerably above usual normal limits.

Another line of evidence linking hypercalciuria and calcium stone disease is that treatment of hypercalciuria with oral thiazide diuretics greatly reduces the rate of new stone production. Thiazides stimulate distal tubule calcium reabsorption [19] and reliably lower urine calcium excretion in humans [20] and in rats [21]. Chronic thiazide administration lowers calcium oxalate supersaturation in parallel with the decreasing urine calcium excretion (Fig. 3), and as a consequence might be expected to prevent calcium stone formation. Our data [1] and those of others [22] show a decrease in new stone production during treatment with thiazides (Fig. 4).

Pathogenesis of hypercalciuria. Calcium stone disease ensuing from hypercalciuria can be treated with thiazides, or a low-calcium diet or agents such as sodium cellulose phosphate that chelate dietary calcium and interfere with its absorption from the intestinal lumen [23]. Probably any treatment that lowers urine calcium excretion will reduce stone recurrence, but the long-term systemic effects of a given treatment may depend on the interaction between the influence of the treatment on calcium metabolism and the underlying physiologic disorders responsible for hypercalciuria. Genetic hypercalciuria is such a complex amalgam of intestinal and renal disorders that its pathophysiologic basis is far from obvious.

Virtually everyone with the syndrome absorbs dietary calcium at an accelerated rate (Table 4). Hyperabsorption would tend to raise blood calcium concentration, increase the postprandial filtered load of calcium, and suppress secretion of parathyroid hormone (PTH). The fall in PTH secretion in turn would reduce renal tubular calcium reabsorption [24]. One would predict from this sequence that the resulting hypercalciuria would best be treated by the use of a low-calcium diet or the administration of sodium cellulose phosphate. Even fasting urine calcium levels are elevated in most patients, however [25], and fasting values for fractional renal calcium reabsorption are reduced [26, 27]; these findings suggest that the kidney's ability to conserve calcium is less than normal.

When we challenged patients who have idiopathic hypercalciuria by giving them a low-calcium diet for 9 days [28], urine calcium losses were abnormally large (Fig. 5), and calcium excretion frequently exceeded intake. Because these patients also failed to conserve phosphate and magnesium as effectively as did normals (Table 5), one can infer that tubular reabsorption or bone metabolism of all three ions was abnormal. Only the small fraction of patients who did conserve calcium normally could be considered for therapy with a long-term low-calcium diet or cellulose phosphate; most patients would be better treated with thiazides. Today's patient excreted 3.6 to 3.8 mg/kg/24 hr of calcium while ingesting 1.9 to 2.1 mg/kg/24 hr, and he clearly is in the group that would not be best treated with cellulose phosphate or a low-calcium diet, but may benefit from thiazide.

Chronic thiazide therapy, however, is not without risk. Zerwekh and Pak have found persistent calcium overabsorption (estimated from unidirectional mucosal to serosal ^{47}Ca movement) during long-term thiazide therapy in a majority of patients with hypercalciuria [29]. The only patients whose absorption rates fell were those who had elevated serum PTH or urine cAMP levels. These patients presumably had a predominant renal tubular transport defect for calcium reabsorption that provoked secondary hyperparathyroidism, increased serum levels of $1,25(OH)_2D_3$, and produced calcium overabsorption. Because none of the patients we studied had elevated PTH (Fig. 5) or cAMP levels [28], we suspect that thiazides could cause chronic calcium retention.

There is evidence that thiazide can induce calcium retention in the rat. We increased intestinal calcium absorption by giving rats subcutaneus $1,25(OH)_2D_3$ [21]. Urine calcium excretion increased from an average value of 1.5 to 12.8 mg/24 hr; virtually all of the increase was due to increased dietary calcium absorption, as evidenced by the observation that a low-calcium diet reduced urine calcium excretion to 0.8 mg/24 hr. When chlorothiazide was given to rats receiving $1,25(OH)_2D_3$ and

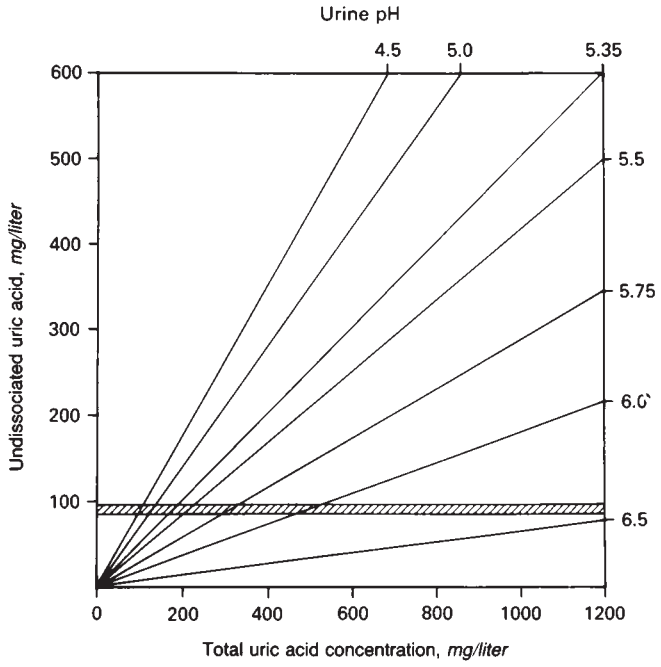

Fig. 1. *Nomogram showing undissociated uric acid concentration at values of urine pH and total uric acid concentration.* The solubility limit for uric acid is shown by crosshatched bars (96 ± 2 mg/liter).

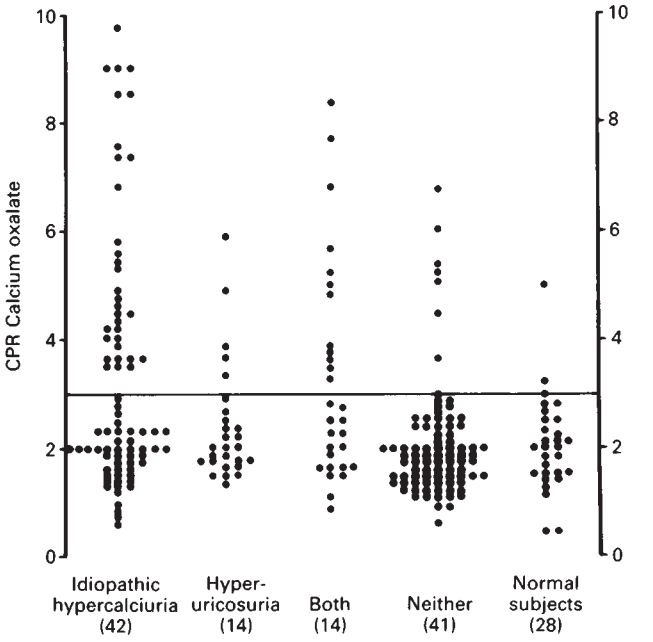

Fig. 2. *Calcium oxalate concentration product ratio (CPR) in 24-hour urine collections from 111 calcium stone formers and 28 normal subjects.* Each point represents a single urine sample. The number of patients in each category is shown in parentheses. One normal subject was studied twice and had urine CPR values of 3.2 and 5.2. The rest each contributed one urine value to the figure. Forty patients elaborated at least one urine sample with CPR above 3: 22 had hypercalciuria, 3 had hyperuricosuria, 9 had both, and 6 had neither. (From Ref. 1.)

eating normal chow, mean urine calcium fell from 12.8 to 6.6 mg/day. We found no evidence from studies of everted gut sacs that chlorothiazide caused a concomitant reduction in intestinal calcium absorption in these animals, however. Colonic calcium transport, measured in the Ussing chamber, also was unaltered when chlorothiazide was added to the medium. One can infer from this series of observations that approximately 6 mg/day of calcium was being absorbed and not excreted. If these data can be extrapolated to humans, and if studies of segmental transport predict overall intestinal absorption, thiazides might cause calcium retention in patients with nephrolithiasis.

Despite these experimental findings, the balance of evidence favors thiazide therapy for idiopathic hypercalciuria. The alternative, treatment with a low-calcium diet, seemed to deplete total-body calcium stores, at least over the short term, in our studies [28]. Chronic calcium accumulation during thiazide therapy has not been documented in humans with hypercalciuria. If it does occur, it might not even be disadvantageous, provided the calcium accumulates in bone. A key experiment that has not yet been performed in patients with hypercalciuria is administration of a low-calcum diet over many months, with intermittent measurement of the precise levels of intake and excretion to determine whether negative calcium balance persists. Perhaps immediate losses are from unessential stores that are readily mobilized, whereas structural bone mineral is better protected. Another key experiment that should be done is determination of the effects of thiazides on external calcium balance in patients with genetic hypercalciuria.

Role of hyperoxaluria. Although not a substrate for mammalian enzymes, oxalic acid is produced from glycolate. Also, dietary oxalate is absorbed by the gut at a rate of approximately 2 to 6 mg/day in normal individuals [30]. The urine is the only vehicle for excretion, and urinary oxalate concentration normally varies between 100 and 400 μM [1]. Urine calcium concentration normally varies between 3.0 and 7.5 mM. Using the extremes of both ranges to calculate chemical concentration products yields values of 3×10^{-7} and 30×10^{-7} M^2, respectively. The *equilibrium* solubility product (Ksp) for calcium oxalate monohydrate is only about 2.3×10^{-9} M^2 [31]. Thus, normal levels of urinary calcium and oxalate could exceed the Ksp by more than 100-fold [1].

The large driving force for crystal formation implied by this calculation is offset by formation of complexes and by at least one substance in urine that interferes with the growth of calcium oxalate crystals. Were it not for these offsetting influences, even normal urine would produce crystal most of the time. Calcium forms soluble salts in urine mainly with citrate and phosphate. As a result, ionic calcium is reduced to only about 50% of the total calcium concentration [32]. Oxalate forms a sodium salt, which represents as much as 40% of the total oxalate in urine, as well as some soluble calcium salts. Therefore, ionic oxalate probably is reduced to about 40% of the total. Because of these soluble complexes, the final product of the urine calcium and oxalate ion activities is not more than 20% to 25% of the chemical concentration products [33]; still, this value is far above the Ksp.

Despite the supersaturation, normal urine can inhibit crystal development so effectively that calcium oxalate crystals are not usually seen. This inhibitory power might reside in a specific glycoprotein that has very unusual properties [31, 34, 35]. The protein weighs about 14,000 daltons. It is strongly acidic, in part

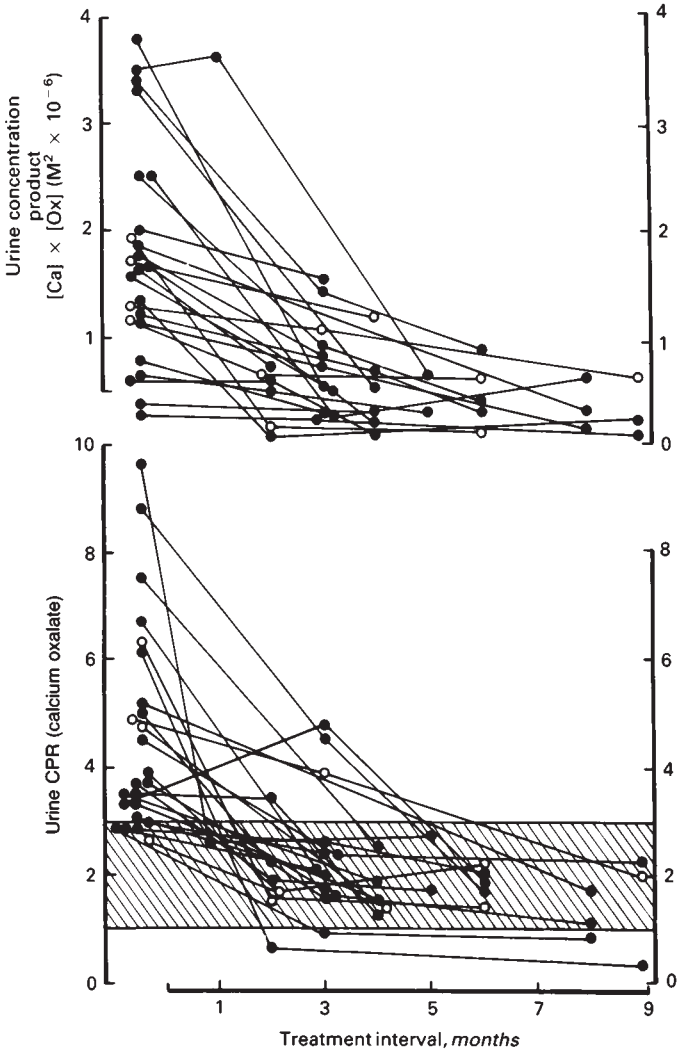

Fig. 3. *Effects of thiazide treatment on 24 patients whose pretreatment 24-hour urine concentration product ratio (CPR) exceeded 3.* Four patients (*open circles*) were not hypercalciuric; the remainder (*closed circles*) were. The average pretreatment values of concentration product ratio (*lower panel*) and concentration product (*upper panel*) are shown as well as each set of values obtained during treatment. Thiazide treatment lowered concentration product ratios progressively in every patient; urine concentration product also tended to decline, especially when it had been very elevated before treatment. (From Ref. 1.)

because aspartic and glutamic acids predominate over lysine and arginine and probably because it contains γ-carboxyglutamic acid as well. The protein seems to act as an inhibitor by adsorbing to crystal surfaces [34], but the details of this action are unknown.

Hyperoxaluria, like hypercalciuria, raises the urine ion activity product and upsets the normal balance between supersaturation and inhibition, so crystals are more likely to form. An increase in oxalate concentration increases supersaturation even more than an equivalent increase in calcium concentration does [36], perhaps because oxalate forms fewer soluble salts in urine; any increase in oxalate chemical concentration therefore is more directly translated into increased supersaturation.

The main reasons for hyperoxaluria are dietary excess and intestinal disease. Hereditary disorders of metabolism rarely cause primary oxalate overproduction; dietary excess usually arises from ingestion of foods that contain more than 0.1% oxalate by weight. For an intestinal disease to cause hyperoxaluria, it must result in small bowel malabsorption and it must occur in the presence of a functioning colon. Products of digestion and secretion, such as ricinoleic acid or taurocholic acid, usually are absorbed by the jejunum and ileum and do not reach the colon [37]. Ileal disease or resection, however, may permit such materials to reach the colon, where they can increase permeability to oxalate [38]. Lumen oxalate concentrations probably are in the millimolar range, whereas blood levels are about 2 to 4 μM [39], so there normally exists a considerable driving force for absorption that is enhanced when permeability increases. The patient under discussion today was not hyperoxaluric.

Role of defective inhibitors. It seems reasonable to speculate that some people, perhaps because of random genetic variability, produce an abnormally low quantity of inhibitors, or an inhibitor of abnormally low activity, and form calcium stones on this basis. Patients with calcium oxalate stones have been found to have considerably lower values than normal even though their urine was also more supersaturated with respect to that crystal [40]. Quite possibly, reduced inhibitory power leads to stone formation, but this never will be proven until the inhibitory substance is measured directly; such measurements are not yet possible. One observation, however, might link altered inhibition to stone formation. Young children produce a protein that has stronger inhibitory properties than that of adults, and children—even those with hypercalciuria—rarely produce calcium oxalate stones [41]. The peak age of onset for stone production is 18 to 20 years, just after growth ceases [42]. No measurements of inhibitory activity were made for the patient under discussion, so the role of reduced inhibition in his disease is unknown.

Role of heterogeneous nuclei. Hypercalciuria and hyperoxaluria raise urine supersaturation and produce a milieu conducive to crystallization. But the zone of metastability for calcium oxalate monohydrate (which extends from the Ksp to the activity product that produces an apparent solid phase) encompasses an 8-fold range in artificial buffers and a 12-fold range in urine. This wide range reflects urine inhibition of the growth of crystal nuclei [18]. The metastable zone exists because molecules in solution tend to distribute themselves randomly, under the influence of thermal motion, rather than aggregate in crystals. The only reason that crystals do form is that, by chance alone, atoms inevitably coalesce into momentary, transient clusters; when they approach each other closely, attractive forces between calcium and oxalate (mainly hydrogen bonding) counteract the tendency each atom has to fly away again. The total binding force increases with the size of the cluster, so the largest ones tend to persist and, by holding on to such new atoms as come by, grow into regular crystals. Supersaturation is a measure of atomic crowding in a solution, metastability a reflection of the balance between attractive forces and the escaping tendency of atoms in an aggregate of a given size, weighted by the probability of having aggregates of that size.

Now imagine that, into a metastably supersaturated solution

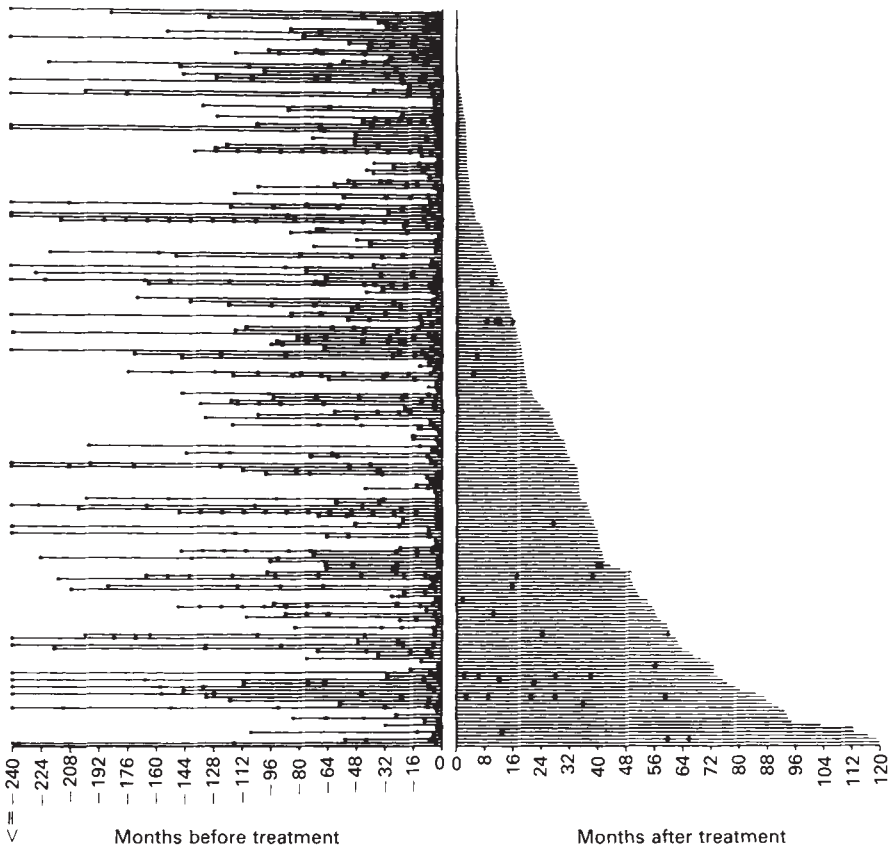

Fig. 4. *Calcium stone formation before and during treatment of hypercalciuria with thiazide.* Each patient is shown as a horizontal line; new stones are designated by closed symbols; multiple stones occurring in cluster are shown as open symbols. (From Ref. 16.)

with an activity product exceeding Ksp by only two-fold, I should add a preformed solid phase of calcium oxalate, already having atoms with considerable internal attractive forces. This solid surface will attract new atoms and grow, because the density of mobile ions in solution will cause more atoms to bombard the surface than can disengage themselves and escape; the fact of crystal growth in a solution that cannot create a new solid phase do novo is the very definition of solution metastability. Stated more technically, addition of a solid phase abridges the thermodynamically costly process of nucleation and permits the formation of more stable aggregates.

Because new crystal nuclei are very small, the urine that flows continuously from tubule orifices into the bladder sweeps away all but those large enough to lodge in some crevice or occlude the lumen of a terminal collecting duct. Clinical nephrolithiasis depends upon collecting nuclei into large crystal aggregates. Newly formed microcrystallites can adhere to the surfaces of preformed crystals. If the conditions are right and if the preformed surface is much larger than the microcrystallites, the surface can serve as an organizing template that holds many microcrystallites together, thus producing sizable aggregates.

The idea that added crystals of calcium oxalate can promote calcium oxalate nucleation and foster development of even larger crystals is, of course, a circular notion; there are no preformed calcium oxalate crystals in the kidneys or urine unless supersaturation is extreme enough to produce them—and they would not be large unless they grew that way. But evidence does indicate that the surface of an entirely different crystal, uric acid, can substitute for the surface of calcium oxalate, permit crystal formation at low degrees of calcium oxalate supersaturation, and serve as a template for microcrystallite organization [43, 44].

The fate of uric acid crystals bathed in a solution containing uric acid, calcium, and oxalate is influenced by the solution's concentration of undissociated uric acid ([HU]). If [HU] is below 96 mg/liter at 37°C, the uric acid crystals dissolve. If [HU] exceeds 96 mg/liter, uric acid competes with calcium and oxalate for the crystal surface, and competition is governed by their relative supersaturations. Conditions best suited to the formation of calcium oxalate surface are found in a solution supersaturated slightly with HU and strongly with respect to calcium oxalate. Very high [HU] causes growth of uric acid crystals alone. A high degree of supersaturation with respect to both favors mixed crystals of uric acid and calcium oxalate, like those in today's patient.

Among calcium oxalate stone formers, hyperuricosuria appears almost as commonly as does hypercalciuria [45–47] and seems mainly due to a high intake of meat, fish, and poultry. Indeed, this was the cause of the hyperuricosuria in the patient described today. Patients with hyperuricosuria and calcium oxalate stones excrete urine that is more supersaturated with respect to uric acid than normal urine or urine of patients with hypercalciuria alone (Table 6), partly because their high meat intake lowers urine pH. When we reduced uric acid excretion with allopurinol, we found [45] that production of new calcium oxalate stones decreased greatly (Fig. 6); this observation has been confirmed by others [48].

In hyperuricosuric calcium oxalate nephrolithiasis, we have a

Table 4. Intestinal calcium absorption in normal subjects and in patients with idiopathic hypercalciuria*

Reference	Method	Calcium intake *(mg/day)*	Percentage of dietary calcium absorbed	
			Normals	Patients
Cannigia et al 1964	Fecal ^{45}Ca	Free**	—	22.0 (1)***
Birge et al 1969	^{47}Ca po/iv	800	52.2 ± 13.2 (6)	58.5 ± 8.6 (4)
Wills et al 1970	^{47}Ca po/iv	400	49.0 ± 10.0 (4)	76.0 ± 17.0 (5)
Pak et al 1972	Fecal ^{47}Ca	400	45.6 ± 9.0 (29)	69.7 ± 7.0 (9) 58.1 ± 13.0 (11)†
Pak et al 1974	Fecal ^{47}Ca	400	50.0 ± 7.0 (20)	71.7 ± 7.0 (22)‡ 50.0 ± 17.0 (2)§
Ehrig et al 1974	$^{47}Ca/^{45}Ca$ po/iv	462–952	—	47.8 ± 11.0 (22)†† 37.6 ± 11.0 (22)§§
Kaplan et al 1977	Fecal ^{47}Ca	400	48.0 ± 8.0 (11)	80.0 ± 9.0 (211)‡ 73.0 ± 7.0 (3)§
Shen et al 1977	$^{47}Ca/^{45}Ca$ po/iv	Free**	27.0 ± 9.0 (14)	40.0 ± 9.0 (15)
Barilla et al 1978	Fecal ^{47}Ca	400	None studied	69.5 ± 6.4 (10)‡ 70.1 ± 10.4 (8)§
Zerwekh et al 1980	Fecal ^{47}Ca	400	None studied	69.0 ± 7.0 (11)‡ 68.0 ± 9.0 (10)§

* Values are mean ± SD. Reprinted from Ref. 46.
** Usual diet was not measured.
*** Numbers in parentheses indicate patients studied.
† Eleven patients listed as having normocalcemic primary hyperparathyroidism may be considered hypercalciuric.
‡ "Absorptive" idiopathic hypercalciuria.
§ "Renal" idiopathic hypercalciuria.
†† Prior to therapy.
§§ 3–16 months after hydrochlorothiazide therapy began.

clear instance of how inheritance and environment can interact to produce disease. Our hypothesis is that hypercalciuria is not a disease but a reflection of a genetic variability that causes a high traffic of calcium through the bodies of many people; we have no reason to believe that the genetically determined range of urine calcium excretion has varied much over centuries. The level of urinary uric acid, however, is mainly determined by culture, which reflects one's ability to afford the cost of a high-meat diet. Moreover, the level can vary greatly. In the United States, for example, the daily intake of meat products increased from 7 to 11 ounces per person between 1905 and 1975 [49]. Duing the same period, widespread use of refrigeration made fresh fruits and vegetables available year round and resulted in a steadier intake of oxalate. For those people who inherit a tendency toward hypercalciuria, an increased oxalate intake results in higher urine supersaturation, and a higher meat intake causes increased uric acid excretion and lower urine pH. Supersaturation is the tinder; uric acid crystals are the match. Today's patient, whose hyperuricosuria was clearly of dietary origin, illustrates this phenomenon very well.

Mixed calcium oxalate and uric acid stones

The patient under discussion produced two types of crystals at least partly because he produced urine that was abnormally supersaturated with respect to both uric acid and calcium oxalate. Increased uric acid, moreover, could well have fostered the formation of calcium oxalate stones. This patient is representative of a large group of patients we have studied (Fig. 7) [10]. Patients like this one have doubly supersaturated urine; those with either calcium oxalate or uric acid stones show an imbalance in supersaturation that favors one crystal over the other. Balanced supersaturation must favor mixed stones given that crystals of uric acid and calcium oxalate share an identical pattern of surface charges; because chance variations of supersaturation dictate which phase grows, random layers form, first one crystal and then the other.

In terms of stone production rate and morbidity, calcium oxalate stone formers and uric acid stone formers are at the extremes of a range nearly bisected by patients who form mixed stones (Table 7) [10]. Why uric acid stones recur more frequently is unknown, but it could be because urine has little effect on uric acid solubility or crystal growth.

Both abnormalities of urine chemistry should be corrected, because either can give rise to stones. In most instances, increased calcium oxalate supersaturation results from genetic hypercalciuria (which is treatable with thiazides), primary hyperparathyroidism, dietary hyperoxaluria, or low fluid intake. Elevated uric acid supersaturation always reflects low urine pH, elevated total uric acid concentration, or both. Dual treatment with thiazides and allopurinol tends to protect against new stones (Table 7), as one would expect. The patient presented today had hypercalciuria, which might not have responded well to a low-calcium diet, but it should have responded well to thiazide. His hyperuricosuria, low urine pH, and increased urine concentration of undissociated uric acid responded well to reduced purine intake, which can be an ideal treatment. If he had not agreed to alter his diet, allopurinol therapy would have been a rational alternative.

Questions and answers

DR. JEROME P. KASSIRER: Many physicians, of course, do not have ready access to a laboratory sophisticated enough to

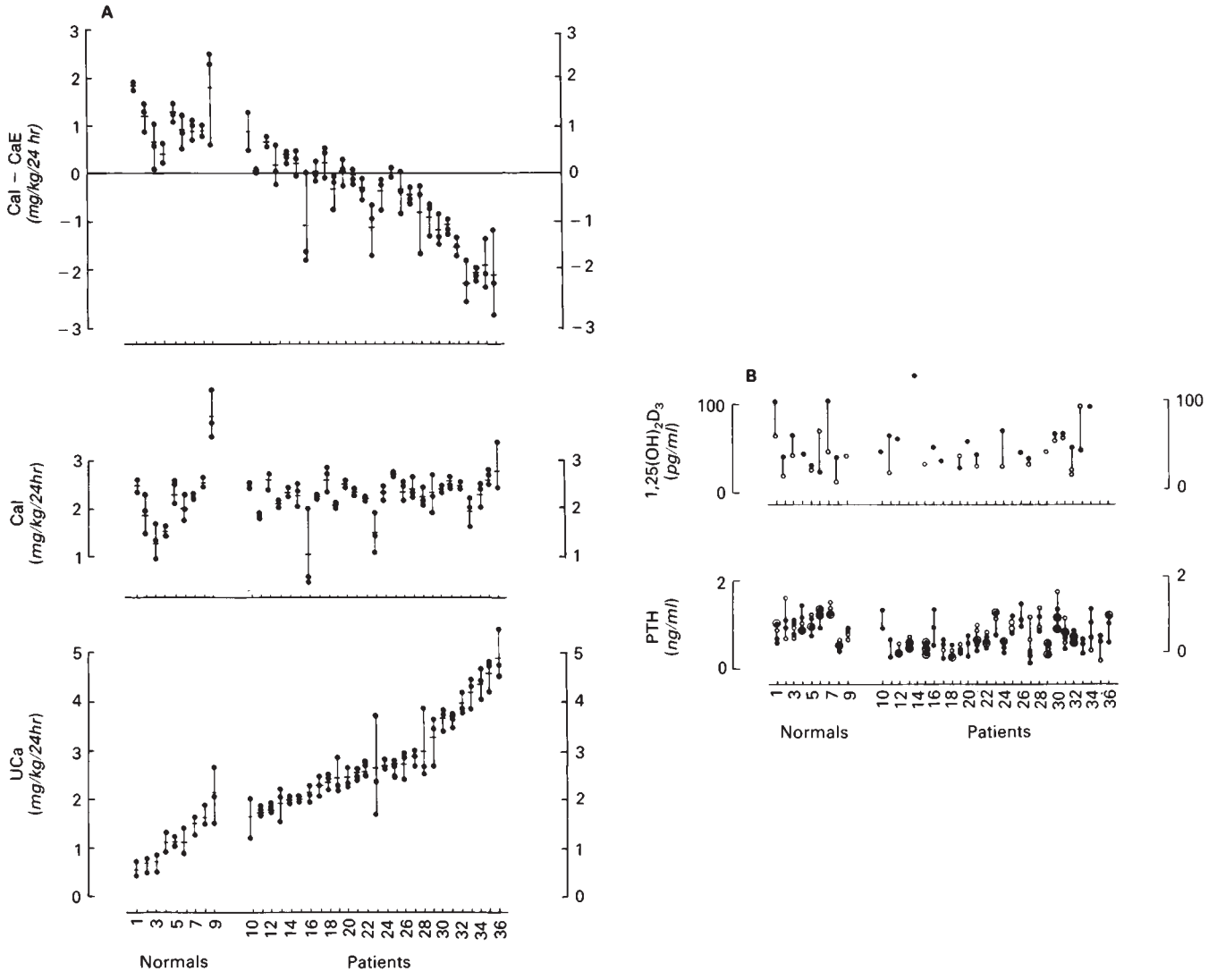

Fig. 5. *Calcium intake and excretion* (**A**) *and serum PTH and 1,25(OH)$_2$D$_3$* (**B**) *values in patients and normal subjects.* Urine calcium excretion (UCa) and intake (CaI) were measured during a period of low-calcium diet. Serum values obtained during both low-calcium diet (●) and free-choice diet (○) are shown. Normal subjects and patients are shown in order of ascending mean calcium excretion. Patients 24 and 26 were mothers of patients 16 and 36, respectively. Mean calcium intakes of normal subjects (2.29 ± 0.15 SEM) and patients (2.31 ± 0.05) did not differ significantly. Mean excretion rates during low-calcium diet for normals (1.18 ± 0.11) and patients (2.87 ± 0.11), and values of intake minus excretion (CaI−CaE) for normals (1.14 ± 0.12) and patients (−0.58 ± 0.11) differed significantly from each other ($P < 0.001$ for both). Similarly, calcium excretion in normal subjects (1.78 ± 0.16) and patients (4.38 ± 0.15) during free-choice diet (not shown) differed from each other ($P < 0.001$) and from values during low-calcium diet ($P < .01$ for both normal subjects and patients). (From Ref. 28.)

examine renal stones in such detail. Is it possible for us to adequately evaluate patients who form multiple stones if we use fewer than the full array of elegant studies you described? For example, should we routinely measure parathyroid hormone? Should we always do the CPR test? Or would the simple measurement of 24-hr urine calcium and uric acid with the patient on a normal diet be sufficient?

Dr. Coe: Ideally, every patient with a calcium oxalate kidney stone should have the 24-hr urine calcium and serum calcium concentrations measured as accurately as possible. Uric acid excretion also should be measured, but one must remember that erroneous values can obtain if techniques designed to measure serum rather than urine uric acid are used. A specialized laboratory such as ours probably is best reserved for the study of patients in whom a clear diagnosis of hypercalcemia, hypercalciuria, or hyperuricosuria cannot be made routinely. Urine oxalate is difficult to measure at the moment, and I would not advise that routine oxalate screening be done.

Dr. Mark Shields (*Attending Physician, Michael Reese Hospital*): Most of the data you have presented concern patients with multiple, recurrent stones. A common problem facing the clinician is how aggressive one should be in evaluating and treating patients who have had only a single stone. What do you recommend under such circumstances?

Dr. Coe: We have observed that patients with a single stone also have metabolic disorders with the same frequency as do patients with multiple stones [50]. During treatment, these patients suffer a relapse of stone disease at roughly the same

Table 5. Phosphorus and magnesium values in normal subjects and in patients with idiopathic hypercalciuria[a]

Measurement	Normal subjects		Patients	
	Low-calcium diet	Free-choice diet	Low-calcium diet	Free-choice diet
Serum phosphorus[b]	3.41 ± 0.68	3.41 ± 0.60	3.22 ± 0.06	3.22 ± 0.06
Phosphorus intake[c]	10.9 ± 0.60	—	10.6 ± 0.30	—
Phosphorus excretion[c]	8.94 ± 0.41[d]	11.5 ± 0.6	11.6 ± 4[e,i]	13.9 ± 0.5[h]
Cp/Ccr (%)[f]	11 ± 1	14 ± 1	17 ± 1[i]	19 ± 1
Serum magnesium[b]	1.98 ± 0.02	1.93 ± 0.02	1.97 ± 0.02	2.01 ± 0.01
Magnesium intake[c]	2.32 ± 0.65	—	2.25 ± 0.06	—
Magnesium excretion[c]	1.11 ± 0.44	1.3 ± 0.1	1.32 ± 0.04[e,h]	1.57 ± 0.65[g]

[a] Reprinted from Ref. 28.
[b] Serum values are measured in mg/dl.
[c] Intake and excretion are measured in mg/kg/24 hours.
[d] Differs from free diet; $P < 0.02$.
[e] Differs from free diet; $P < 0.001$.
[f] Cp/Ccr refers to phosphate clearance/creatinine clearance.
[g] Differs from normal, same diet; $P < 0.05$.
[h] Differs from normal, same diet; $P < 0.01$.
[i] Differs from normal, same diet; $P < 0.001$.

Table 6. Summary of urinary uric acid saturation measurements[a]

24-hour urine values	Metabolic group				
	Normal ($N = 20$)	IH ($N = 24$)	HU ($N = 12$)	Both ($N = 14$)	Neither ($N = 17$)
No. of samples	24	69	36	42	51
Total uric acid, *mg/liter*	503 ± 32	421 ± 23	575 ± 28	616 ± 27[g]	462 ± 32
Urine volume, *ml*	1268 ± 65	1717 ± 133[h,j]	1501 ± 79[f]	1397 ± 70	1387 ± 90
Urine pH	6.22	5.92	5.62[g]	5.74[g]	5.67[h]
Undissociated uric acid[b], *mg/liter*	57 ± 8[j]	84 ± 11	155 ± 21[h]	150 ± 16[i]	128 ± 18[g]
CPR, monosodium urate	2.8 ± 0.3[e]	2.2 ± 0.2	2.7 ± 0.2	3.1 ± 0.2	2.2 ± 0.2
Initial [Na] · [urate][c], $M^2 \times 10^{-5}$	37 ± 4	27 ± 3	35 ± 4	42 ± 3[j]	29 ± 3
Final [Na] · [urate][d], $M^2 \times 10^{-5}$	13.2 ± 0.7	11.0 ± 0.5	12.0 ± 0.6	12.9 ± 0.5	13.2 ± 1.0
Sodium concentration, *mEq/liter*	131 ± 8[j]	118 ± 7	130 ± 7	149 ± 7[k]	132 ± 7[j]

[a] All values, except for the numbers of samples and the numbers of people in each metabolic group (in parentheses), are the means ± SEM. Abbreviations used are: IH, idiopathic hypercalciuria; HU, hyperuricosuria; CPR, concentration product ratio; [Na], sodium concentration (mEq/liter); [urate], urate concentration (mmoles/liter). Reprinted from *Kidney International* (Vol. 17, 1980 with permission) [3].
[b] The mean equilibrium value, determined in 26 urine samples of pH below 5.6, after 48 hours of incubation with crystals of uric acid, was 90 ± 5 mg/liter.
[c] Before incubation with crystals of sodium hydrogen urate.
[d] After 48 hours of incubation with crystals of sodium hyrodgen urate.
[e] Based upon the study of the 16 of the 20 normal subjects who had CPR measurements.
[f] $P < 0.05$, compared with control.
[g] $P < 0.02$, compared with control.
[h] $P < 0.01$, compared with control.
[i] $P < 0.001$, compared with control.
[j] $P < 0.05$, men vs. women.
[k] $P < 0.02$, men vs. women.

rate. There are no satisfactory prospective studies of the natural history of untreated solitary stone disease, but two retrospective studies that I have reviewed elsewhere suggest that most of these patients ultimately become recurrent stone formers [47]. In other words, the solitary stone former usually is someone destined to be a recurrent stone former.

DR. JORDAN J. COHEN: Is there a role for measuring plasma ionized calcium? Can it help distinguish intestinal versus renal hypercalciuria? And is it useful in identifying patients with mild hyperparathyroidism in whom serum calcium levels might not be clearly elevated?

DR. COE: Ionized calcium measurements are neither intrinsically more accurate nor more discriminating than are measurements of total serum calcium, as far as I know. In our study of hyperparathyroid stone disease, we observed that a large fraction of the patients referred to us had serum calcium levels that were elevated by our standards, but only to the range of 10.1 to 10.5 mg/dl [51]. Such patients would be classified as "normocalcemic" in a laboratory with a wider range of normal. I suspect that as clinical laboratories become more sophisticated in measuring serum calcium and as their ranges of normal shrink, diagnosing primary hyperparathyroidism will be no easier using ionized calcium, especally if patients with serum calcium levels above 10.1 mg/dl have repeated serum calcium measurements.

DR. KASSIRER: Most people find it difficult to change their

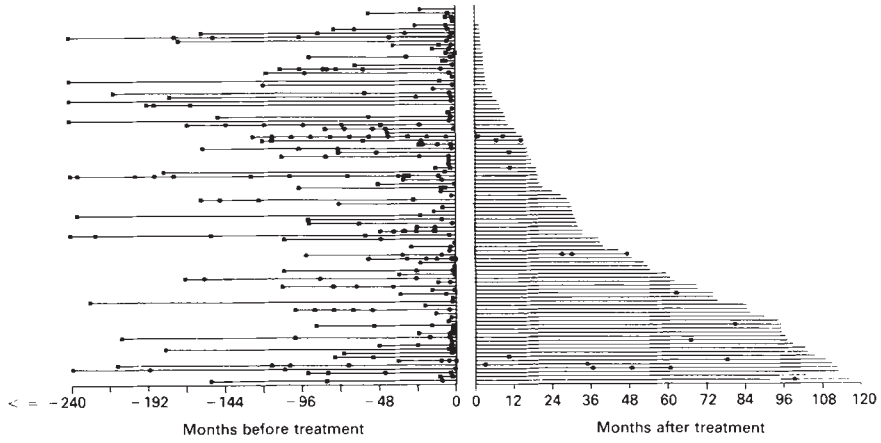

Fig. 6. *Calcium stone formation before and during treatment of hyperuricosuria with allopurinol.* Each patient is shown as a horizontal line; new stones are represented as closed symbols; and multiple stones in clusters are illustrated as open symbols.

dietary habits, and they often choose not to do so. In patients who form uric acid stones, an alternative to the lifelong ingestion of a restricted protein intake is allopurinol therapy. If patients were given the choice and were told precisely what the risks of allopurinol were—and I think the hazards are relatively small—these patients might choose to take the drug rather than follow a diet. Shouldn't the choice of treatment be made by the patient?

DR. COE: If a patient won't accept the recommendation to reduce meat, fish, and poultry intake, treatment with allopurinol is the only rational alternative. I agree with you that the risks of allopurinol are few and that patients who reject dietary protein restriction should have the drug.

DR. KASSIRER: Does one really need to do any fancy urinary studies in patients who form uric acid stones or calcium oxalate stones? If we use a few screening tests to rule out serious diseases and we also have the information from the stone analysis, why not simply treat all the patients?

DR. COE: The notion of treating all patients who form calcium oxalate stones and studying only those who relapse during treatment is an intriguing and, I think, a legitimate topic for study. One could compare the results of such a strategy with the conventional approach, but I would raise certain cautions. Specific treatment is necessary in patients with hypercalcemia, intestinal disease and oxaluria, renal tubular acidosis, and also in patients who may harbor underlying systemic diseases with disordered divalent mineral metabolism, such as hyperthyroidism, rapidly progressive bone disease, Cushing's syndrome, or sarcoidosis. Even if that is done and one is left with normocalcemia in otherwise healthy people who form calcium stones, one still must decide whether to treat these people with thiazide alone, thiazide and allopurinol, or thiazide and a low-purine diet. Should one routinely lower dietary oxalate intake, even though most patients are not hyperoxaluric? Overall, there are uncertainties about treating without pretesting, and I submit that the matter requires a prospective study.

DR. DAVID BUSHINSKY (*Staff Nephrologist, Michael Reese Hospital*): In your balance studies you showed that at least one-half of your patients with idiopathic hypercalciuria were in negative calcium balance. If negative calcium balance persisted daily over long periods, one might expect to see the development of either osteoporosis or other metabolic bone disease. Do patients with idiopathic hypercalciuria have an abnormally high frequency of bone disease?

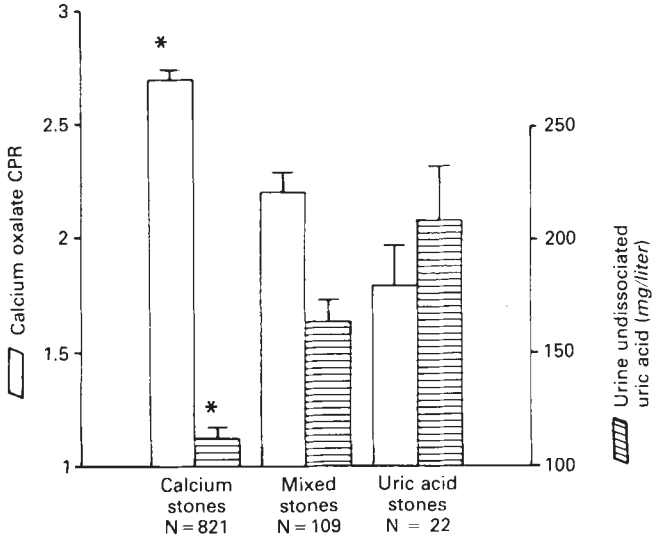

Fig. 7. *Calcium oxalate and undissociated uric acid supersaturation in stone-forming patients.* Values above 1 for CPR (*open bars*) indicate supersaturation. The solubility of undissociated uric acid (*hatched bars*) in urine is 96 ± 3 mg/liter; hence, relative supersaturation can be calculated by dividing the values shown by 96. The CPR values were obtained from 431 patients with calcium oxalate, 56 with mixed calcium oxalate and uric acid, and 9 with pure uric acid stones; corresponding numbers of patients providing values for undissociated uric acid were 811, 106, and 22. All values are mean ± SEM. Asterisks indicate that the values differ from the respective levels in both mixed and uric acid stone groups; $P < .001$. (Reprinted from *Kidney International*, (Vol. 22, 1982 with permission) [10].

DR. COE: The negative calcium balance we observed was manifested while the patients followed a diet extremely low in calcium. Normal diets provide much more calcium, and negative calcium balance would not be expected.

DR. IRVING ZITMAN (*Attending Physician, Michael Reese Hospital*): Is it important that we know how much water a person with nephrolithiasis takes in?

DR. COE: The 24-hr urine volume gives an excellent estimate of water intake in relation to need. It is best that patients with recurrent stone disease have a urine volume of at least 1500 ml/day, and fluid intake should be adjusted appropriately.

DR. COHEN: How effective is thiazide therapy in the normocalciuric patient who forms calcium stones?

Table 7. Clinical characteristics of patients with calcium, uric acid, or mixed stones[a]

	Type of stone		
	Calcium	Mixed	Uric acid
Number of patients (males, females)	821, 197	109, 20	22, 4
Number with multiple stones	646	101	17
Age at first stone (year)	36	36	46
Pretreatment interval (pt year)[b]	5770	1072	88.2
Total recurrent stones	4946	1254	224
Recurrent stones/100 pt years	85.7	117[b]	254[b,c]
Hospitalizations/100 pt yrs	25.4	29.9[b]	31.7[b]
Cystoscopies/100 pt yrs	13.8	21.8[b]	19.2[b]
Infections/100 pt yrs	6.9	4.4[b]	2.3[b]
Surgeries/100 pt yrs	7.8	5.5[b]	10.2[b,c]
Treatment interval (pt yrs)		313	71
Total new stones		48	12
Patients with new stones		13	2
Predicted stones		366	180
% of patients stone free		88	91

[a] Reprinted from *Kidney International* (Vol. 22, 1982 with permission) [10].

[b] Total years between onset of first stone and institution of treatment for each patient multiplied by the total number of patients forming calcium oxalate, mixed calcium oxalate and uric acid, or pure uric acid stones.

[c] Differs from calcium, $P < .001$.

[d] Differs from mixed, $P < .001$.

[e] Percentage of patients stone free for this group [4, 11, 17] has averaged 89%.

DR. COE: Our studies [46] and studies by Pak et al [52] and Maschio and colleagues [53] have included some patients who do not have frank hypercalciuria. Treatment results seem indistinguishable from those observed in patients with hypercalciuria. This finding is not surprising given that thiazides lower urine calcium excretion even in normocalciuric people, and that risk of stone formation is increased by levels of calcium excretion within the normal range.

DR. COHEN: Does the effect of thiazide vary in relationship to the amount of salt in the diet? Does a high-salt diet offset the hypocalciuric effect?

DR. COE: High salt intake can increase urine calcium during thiazide treatment [46]. Whether salt loading causes relapse of stone formation despite adequate thiazide therapy is unknown.

DR. GERALD SOBEL (*Attending Physician, Michael Reese Hospital*): Are there circumstances in which manipulating dietary oxalate might be helpful?

DR. COE: Some patients have elevated urine levels of oxalate, that is, above 45 to 50 mg/24 hr, and these individuals have no recognized underlying disease that could predispose to oxaluria. In many such patients, dietary oxalate intake is elevated, and restriction of high-oxalate foods is appropriate.

DR. STEPHEN MICHEL (*Renal Fellow, Michael Reese Hospital*): Do we know what effect thiazide has on intestinal calcium transport?

DR. COE: The only direct data I know of concerning the effect of thiazide on intestinal calcium transport per se have been published by Favus et al [21]. Thiazide does not appear to reduce radiolabeled calcium accumulation by everted gut sacs made from rat intestine, and thiazide does not alter either mucosal-to-serosal or serosal-to-mucosal calcium flux in colon mounted in Ussing chambers. The actual effect of thiazide on overall human intestinal calcium absorption is unknown. To find out what the effects are, one would have to measure total calcium absorption before and after giving the drug.

DR. KASSIRER: Is anything known about the molecular mechanism of thiazide's effect on calcium transport in the renal tubule?

DR. COE: The effect of thiazide on tubular calcium transport has been documented by microperfusion experiments [19], but nothing is known about the molecular mechanism of this transport effect.

DR. CRAIG LANGMAN (*Pediatric Nephrologist, Michael Reese Hospital*): Kidney stones are very rare in children. Why does this disease primarily affect adults?

DR. COE: Renal calculi are indeed much less common in children than in adults. On the other hand, idiopathic hypercalciuria appears to be genetic and is as common in the pediatric population as in the adult population [41]. It is not clear why children are spared from developing stones.

DR. COHEN: In your opinion, are there any stone formers in whom crystalloid excretion is normal and in whom the only defect is an abnormal or absent urinary inhibitor?

DR. COE: We have found that the urine of patients who have renal calculi reduces crystal growth inhibition as compared to urine from normal people [9]. Some stone-forming patients with little crystal growth-inhibiting effect in their urine are not hypercalciuric and do not appear to have excessive supersaturation [40]. Perhaps such patients illustrate an abnormal urinary inhibitor leading to stones. Demonstration of this possibility would require specific measurements of inhibitors by immunoassay or isolation of an abnormal inhibitor.

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